중개의학박사 학위논문

한국 소아청소년에서 발생한 중추 신경계 탈수초 질환의 임상양상, 생물표지자 및 신경계 영상검사에 대한 말이집 희소돌기아교세포 당단백질 항체에 중점을 둔 분석

Clinical Spectrum, Biomarkers, and Neuroimaging of Acquired Demyelinating Syndrome in Korean Children; focusing on Myelin Oligodendrocyte Glycoprotein Antibodies

2020년 8월

서울대학교 대학원

의학과 중개의학 전공

유 일 한

중개의학박사 학위논문

한국 소아청소년에서 발생한 중추 신경계 탈수초 질환의 임상양상, 생물표지자 및 신경계 영상검사에 대한 말이집 희소돌기아교세포 당단백질 항체에 중점을 둔 분석

Clinical Spectrum, Biomarkers, and Neuroimaging of Acquired Demyelinating Syndrome in Korean Children; focusing on Myelin Oligodendrocyte Glycoprotein Antibodies

2020년 8월

서울대학교 대학원

의학과 중개의학 전공

유 일 한

Abstract

Clinical Spectrum, Biomarkers, and Neuroimaging of Acquired Demyelinating Syndrome in Korean Children, focusing on Myelin Oligodendrocyte Glycoprotein Antibodies

Il Han Yoo

Translational, Medicine

The Graduate School

Seoul National University

Acquired demyelinating syndrome (ADS) is an immune-mediated demyelinating event of the CNS, and its symptoms can vary greatly according to the site of inflammation and severity of demyelination. Recent works have reported possible biomarkers, including myelin oligodendrocyte glycoprotein (MOG) antibodies, for ADS diagnosis. This study sought to assess the diagnostic value of the MOG antibody and proposed biomarkers in ADS and determine the spectrum of ADS in Korean children. A total of 94 children with ADS were included. Clinical information, neuroimaging and the status of aquaporin 4 (AQP4) antibodies, as well as the oligoclonal band (OCB) in cerebrospinal fluid, were retrospectively collected. MOG antibodies from sera of patients were identified by a cell-based assay. The biomarker positivity rate was as follows: OCB was found in 4% of patients (2/45), AQP4 antibodies in 7% (5/75), and MOG antibodies in 48% (46/94). MOG antibodies were detected in patients diagnosed

with neuromyelitis optica spectrum disorder (NMOSD)(6/12), acute disseminated encephalomyelitis (17/29), and optic neuritis (7/8). We also found MOG antibodies in patients diagnosed with multiple sclerosis (5/12), unclassified form with relapse (7/12). A diverse distribution of lesions in patients with ADS with MOG antibodies was detected during the follow-up period. The most common lesion locations during the follow-up period were the juxtacortical and subcortical white matter (WM) (57%), Brainstem (46%), cerebellum (43%), optic pathway (43%) and basal ganglia (39%). Compared with patients without MOG antibodies, patients with MOG antibodies had more lesions in the juxtacortical or subcortical area (57% vs. 32%, p = 0.017) and in the optic pathway (43% vs. 21%, p = 0.018). Also, the mean Expanded Disability Status Scale scores were significantly lower in MOG-positive patients than in negative patients ($p < 0.001$). Patients with NMOSD with AQP4 antibodies showed no lesions in the cortex or juxtacortical or subcortical WM. Altogether, our results indicate that MOG antibodies are a more relevant biomarker than OCB in CSF and AQP4 antibodies in Korean children with ADS. MOG antibodies are useful for the diagnosis of relapsing ADS without a definite diagnosis and testing must be performed prior to a diagnosis of MS. Frequent involvement of the cortex and subcortical WM in MOG-positive patients with ADS could lead to a misdiagnosis of MS, and help to differentiate MOG associated disease from NMOSD with AQP4 antibodies.

Keywords: Demyelinating disease, biomarker, myelin oligodendrocyte glycoprotein

Student number:2017-34853

List of Tables

List of Figures

Contents

Introduction

Acquired demyelinating syndrome (ADS) is an acute neurological deficit that results from demyelination of the central nervous system (CNS). ADS phenotypes depend on the clinical symptoms, signs, and supporting neuroimaging information.[1] ADS is a heterogeneous group of diseases that includes a monophasic form and a relapsing form. Pediatric patients with ADS are classified using the International Pediatric Multiple Sclerosis Study Group 2013 criteria.[2] Monophasic ADS is divided into acute disseminated encephalomyelitis (ADEM) and clinically isolated syndrome (CIS) according to the presence of encephalopathy. CIS is defined as the initial CNS demyelinating event without encephalopathy and include various phenotypes according to the involvement of brain or optic pathway or spinal cord. Some CISs can be classified as multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) according to their diagnostic criteria. The relapsing form of ADS includes MS, NMOSD, recurrent optic neuritis (ON), and multiphasic disseminated encephalomyelitis (MDEM). However, not all recurrent ADSs are well classified reliably according to the currently used criteria. For example, the current classification system cannot appropriately diagnose ADEMON.[2] In addition, the diagnosis is made even more difficult in children with recurrent ADS because children with MS have a more atypical presentation than adults.[3] Therefore, there are diagnostic difficulties for some ADSs with

relapse in the early stages of disease.

Given these limitations, recent reports have expanded the role of biomarkers such as oligoclonal band (OCB) in cerebrospinal fluid (CSF), aquaporin 4 (AQP4) antibodies, and myelin oligodendrocyte glycoprotein (MOG).[4-6] In particular, MOG antibodies have been reported to have a high detection rate in pediatric ADS cases, including recurrent ON and ADEM, and AQP4-negative results for NMOSD.[7-11]

In this study, we analyzed clinical features, neuroimaging findings, and the presence of biomarkers in Korean pediatric ADS patients to investigate the diagnostic value of biomarkers and the spectrum of Korean pediatric ADS patients.

Materials and Methods

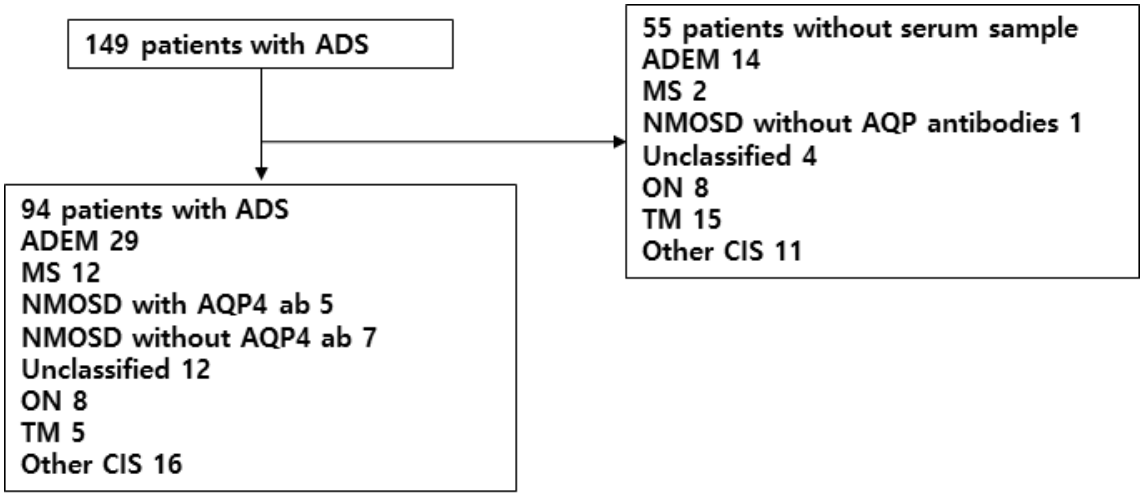
1. Selection and classification of patients

This study was approved by the Institutional Review Board of the Seoul National University Hospital (No.,1811-150-989). A total of 149 patients diagnosed with ADS at the Seoul National University Children's Hospital from March 2013 to May 2018 were recruited; among these, 55 patients were excluded because their sera were not available, resulting in a total of 94 patients. All included patients and their parents provided written informed consent. (Figure.1) We collected clinical information, including age of onset, sex, length of the follow-up period, symptoms and signs at presentation, brain and spine magnetic resonance imaging (MRI) findings, CSF study (white blood cells, glucose, and protein), recurrence, and treatment outcomes. AQP4 antibodies and OCB in CSF were retrospectively collected from electronic medical records. We analyzed brain MRI by dividing it into 11 regions (the cortex, juxtacortical or subcortical white matter, periventricular white matter, deep white matter, corpus callosum, basal ganglia, thalamus and hypothalamus, brainstem, cerebellum, optic pathway, and spine). Based on this information, we divided patients into seven groups [MS, NMOSD, unclassified form, ADEM, isolated ON, isolated transverse myelitis (TM), and other CISs]. The International Pediatric Multiple Sclerosis Study Group 2013 criteria

were used for diagnosing MS, ADEM, and other CISs, and the 2015 revision was used for the NMOSD diagnosis.[2,5] CIS is originally a heterogenous group that included both isolated TM and isolated ON.[2] However, we subdivided CIS into other CISs, isolated ON and isolated TM. The reason is to emphasize the fact that other CIS is a group with brain demyelination without encephalopathy.

Figure 1. The Clinical spectrum and selection of patients

ADS: acquired demyelinating syndrome, ON: optic neuritis, TM: transverse myelitis, MS: multiple sclerosis, NMOSD: neuromyelitis optica spectrum disorder, ADEM: acute disseminated encephalomyelitis, Other CIS: clinically isolated syndrome except for isolated ON or isolated TM, AQP4 ab; auqaporin 4 antobodies



2. MOG-IgG cell-based immunofluorescence assay

Patients′ serum was collected within one month after disease onset and was stored in a liquid nitrogen tank after centrifugation. MOG antibodies were detected qualitatively using a live cell-based indirect immunofluorescence assay. Briefly, MOG-HEK293 cells were seeded into eight-well chambered slides (SPL Life Science, Pocheon, Korea) and incubated in 5% CO_2 at 37C overnight. Cells were blocked with a blocking buffer (1 PBS containing 5% bovine serum albumin) at room temperature for 1 h. The diluted serum (1:20) was added to each of the wells and incubated at room temperature for 2 h. The cells were then fixed using 2% paraformaldehyde at room temperature for 45 mins. After washing, the cells were stained with Alexa-594 (Jackson Immunoresearch, West Grove, PA, USA; diluted 1:2000 with 1 PBS) conjugated anti-human IgG for MOG-IgG for 1 h at room temperature in the dark. The cells were washed three times and then mounted using VECTASHIELD antifade reagent with DAPI (Vector Laboratories, Burlingame, CA, USA).[12] Each experiment was performed in duplicate, and green or red fluorescence in cell membranes was visually examined by the investigators.

3. Statistical Analysis

Continuous variables were analyzed using independent samples *t*-tests. Chi-square or Fisher′s exact tests were used to analyze categorical variables. SPSS software (version 22.0) was used for

statistical analyses, and p-values less than 0.05 were considered statistically significant.

Results

1. Characteristics and seropositivity of ADS patients

A total of 94 patients (male: n = 39; female: n = 55) with ADS were included in this study. The mean onset age of all patients was 101.7 months (SD, 48.7 months). The 28 patients diagnosed with ADEM exhibited encephalopathy as their initial symptom, had polyfocal lesions, and did not experience relapse after three months. One patient was diagnosed with multiphasic ADEM due to encephalopathy relapse three months after onset. Twelve patients diagnosed with MS satisfied the International Pediatric Multiple Sclerosis Study Group criteria. Twelve patients with NMOSD satisfied the 2015 revision criteria of NMOSD; among these, 5 patients tested positive for AQP4 antibodies. Twelve patients were diagnosed with the unclassified form and had one or more relapses after the first attack, but were not diagnosed with either NMOSD or MS. One of the eight patients diagnosed with isolated ON had a recurrence. Five patients diagnosed with isolated TM were monophasic. Other CISs (16 patients) were defined, whether polyfocal or monofocal, as monophasic demyelinating events except for ADEM, and isolated ON, and isolated TM (Figure. 1)

Among the total 94 patients, 46 patients (48%) showed MOG

antibody positivity. Within these MOG antibody-positive patients, ADEM (37%) was the most common diagnosis, followed by the unclassified form (15%), isolated ON (15%), NMOSD (13%; all patients were negative for AQP4 antibodies), MS (11%), and other CIS (9%). However, none of the patients with isolated TM were positive for MOG antibodies. A total of 75 patients were tested for AQP4 antibodies, five of which were positive (5/75, 7%). The clinical diagnosis of these five patients was NMOSD. A total of 45 patients were tested for OCB of CSF, two of which showed positivity (2/45, 4%); one patient was diagnosed with MS and the other with ADEM. The information is summarized in Table 1. A total of 35 (37%) patients among the 94 patients experienced a recurrence, of which 23 were treated with immune suppression or disease modulating regimen. Two patients died as a result of a demyelinating event, and eleven patients showed an EDSS score of more than 4.

Table 1. Demographics, biomarker and clinical features of acquired demyelinating syndrome patients

Patient No	Onset age(months)	Sex	Clinical diagnosis	MOG	AQP4	OCB	Disease course
1	58.9	M	ADEM	+	-	ND*	B**(e)† + myelitis(s)‡ +ON
2	16.1	M	ADEM	+	-	ND	B(e) + myelitis(l)§
3	40.5	F	ADEM	-	ND	ND	B(e) + myelitis(l)
4	44.0	M	ADEM	+	-	-	B(e)
5	29.3	M	ADEM	+	-	ND	B(e)
6	42.7	M	ADEM	-	-	ND	B(e)
7	68.2	F	ADEM	-	-	-	B(e)
8	126.6	M	ADEM	-	ND	ND	B(e)
9	139.0	M	ADEM	+	-	ND	B(e) + myelitis(l)
10	41.4	M	ADEM	-	-	-	B(e) + myelitis(l)
11	40.1	F	ADEM	+	-	-	B(e)
12	68.5	F	ADEM	+	-	ND	B(e) + myelitis(l)
13	160.0	F	ADEM	-	-	-	B(e) + myelitis(l)
14	55.8	M	ADEM	+	-	+	B(e)
15	68.8	M	ADEM	+	ND	ND	B(e)
16	51.8	F	ADEM	+	ND	-	B(e)
17	188.1	F	ADEM	-	-	-	B(e)
18	60.4	M	ADEM	-	-	ND	B(e)
19	63.3	M	ADEM	+	-	ND	B(e) + myelitis(l)
20	73.2	M	ADEM	+	ND	-	B(e)
21	23.4	F	ADEM	-	ND	ND	B(e)
22	9.6	M	ADEM	-	ND	ND	B(e)
23	79.3	F	ADEM	+	ND	ND	B(e)
24	73.5	M	ADEM	+	-	ND	B(e)
25	99.6	M	ADEM	-	-	ND	B(e) + myelitis(l)
26	23.3	F	ADEM	+	ND	ND	B(e)
27	50.2	M	ADEM	+	-	-	B(e) + myelitis(s)
28	38.0	M	ADEM	-	-	-	B(e) → B(e)
29	139.1	F	ADEM	+	-	-	B(e)
30	96.6	M	MS	-	-	-	B(e) → B → B
31	89.2	M	MS	-	-	-	B + myelitis(s) → B(e)
32	129.1	M	MS	-	ND	-	B → B
33	149.7	M	MS	-	-	+	B + myelitis(s) → B
34	112.6	M	MS	+	ND	ND	B → B(e)
35	87.0	F	MS	+	-	-	B → B → B
36	67.0	M	MS	+	-	-	B → B → B
37	111.1	F	MS	-	-	-	B → B + myelitis(l) + ON (unilateral)

38	165.7	M	MS	-	-	-	B
39	33.8	M	MS	+	-	-	B(e) → B
40	65.3	F	MS	-	-	ND	B → B + ON(bilateral)
41	133.9	F	MS	+	-	-	B → B → B
42	119.6	F	NMOSD	-	-	ND	ON(bilateral) + myelitis(l) → ON(unilateral)
43	64.3	F	NMOSD	+	-	-	B + myelitis(l) → B + ON(unilateral)
44	108.5	F	NMOSD	+	-	-	ON(unilateral) + myelitis(l) → B
45	64.8	M	NMOSD	-	+	-	B → B + myelitis(l) + ON(unilateral)
46	39.6	F	NMOSD	+	-	-	ON(bilateral) → B + myelitis(l) → B
47	94.8	M	NMOSD	+	-	ND	B + myelitis(l) → ON(unilateral)
48	120.4	F	NMOSD	+	-	-	Myelitis(l) → B + ON(unilateral)
49	195.9	F	NMOSD	-	+	-	Myelitis(l) → B + bilateral ON
50	126.4	F	NMOSD	-	+	ND	ON(unilateral) + myelitis (l)
51	78.5	F	NMOSD	+	-	-	B + ON(bilateral) → B + Myelitis(l) + ON(bilateral)
52	184.2	F	NMOSD	-	+	-	B + myelitis(l) → B + myelitis(l)
53	108.3	F	NMOSD	-	+	ND	ON(bilateral)
54	75.9	M	Unclassified	-	-	ND	B → B
55	199.4	F	Unclassified	+	-	-	B → B+ myelitis(l)
56	73.2	F	Unclassified	+	-	-	B + ON(bilateral) → B(e)
57	147.3	F	Unclassified	+	-	ND	B → B
58	115.7	F	Unclassified	-	-	-	B + myelitis(l) + B
59	77.1	M	Unclassified	-	-	ND	B(e) → ON(unilateral)
60	125.5	F	Unclassified	-	-	ND	B + ON(bilateral) → B+ ON(bilateral)
61	63.7	F	Unclassified	+	-	ND	B(e) → ON(unilateral)
62	112.0	M	Unclassified	+	-	ND	B + ON(bilateral) → ON(bilateral)
63	121.6	F	Unclassified	+	-	ND	ON(bilateral) → B→ B
64	156.4	F	Unclassified	+	-	-	B(five times)

65	143.2	F	Unclassified	-	-	-	B+ ON(bilateral) + myelitis(s) → B+ ON(bilateral) + myelitis(s)
66	129.2	M	Other CIS	+	-	ND	B + myelitis(l)
67	132.5	F	Other CIS	-	-	-	B
68	108.5	F	Other CIS	+	-	ND	B
69	159.8	F	Other CIS	-	-	ND	B
70	166.6	M	Other CIS	-	-	-	B
71	88.5	M	Other CIS	-	-	ND	B+ ON(unilateral)
72	99.5	F	Other CIS	-	ND	ND	B + myelitis(s)
73	208.4	M	Other CIS	+	-	ND	B
74	209.7	F	Other CIS	-	-	ND	B
75	107.2	F	Other CIS	-	-	ND	B
76	102.1	F	Other CIS	-	-	-	B
77	126.1	M	Other CIS	-	-	-	B
78	65.5	F	Other CIS	-	ND	-	B
79	39.1	F	Other CIS	-	-	ND	B
80	165.2	F	Other CIS	+	ND	ND	B + ON(bilateral)
81	115.4	F	Other CIS	-	-	ND	B
82	126.2	F	TM	-	-	ND	Myelitis(l)
83	149.3	M	TM	-	-	-	Myelitis(l)
84	172.0	F	TM	-	-	ND	Myelitis(l)
85	87.2	F	TM	-	-	-	Myelitis(l)
86	176.6	M	TM	-	ND	ND	Myelitis(l)
87	64.2	M	ON	+	ND	-	ON(unilateral)
88	125.4	F	ON	+	-	ND	ON(bilateral)
89	179.0	M	ON	+	-	ND	ON(unilateral)
90	73.2	F	ON	+	-	ND	ON(bilateral)
91	63.4	M	ON	+	ND	ND	ON(unilateral)
92	168.3	M	ON	+	ND	-	Recurrent ON(unilateral, six

							times)
93	76.9	F	ON	+	_	-	ON(bilateral)
94	144.9	F	ON	-	-	ND	ON(unilateral)

MOG: myelin oligodendrocyte glycoprotein, AQP: aquaporin 4 antibody, OCB: oligoclonal band in Cerebrospinal fluid, ADS: acquired demyelinating syndrome, ON: optic neuritis, TM: transverse myelitis, MS: multiple sclerosis, NMOSD: neuromyelitis optica spectrum disorder, ADEM: acute disseminated encephalomyelitis, Other CIS: clinically isolated syndrome except for isolated ON or isolated TM

*: not done, **:brain demyelination † : with encephalopathy ‡ : 〈 Three vertebral segments, §: ≥ Three vertebral segment

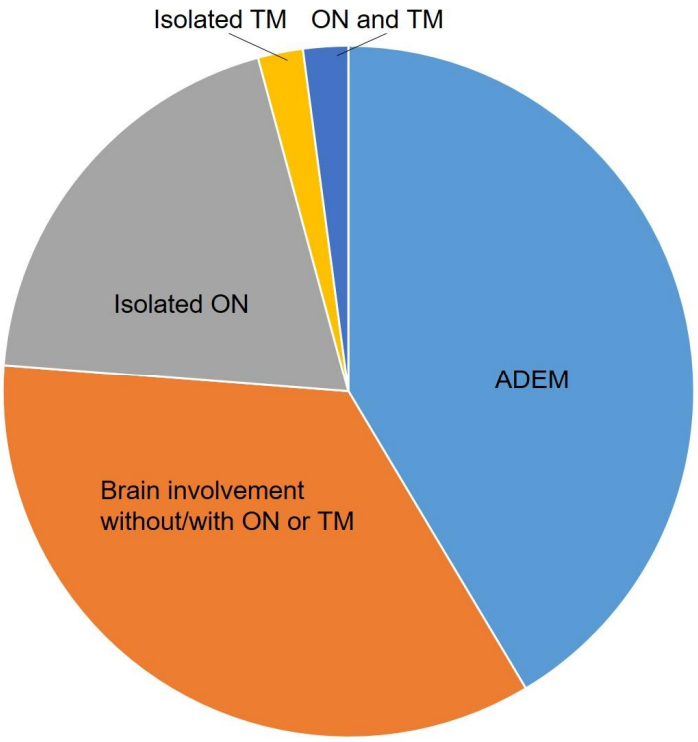
2. Characteristics of MOG antibody-positive ADS patients compared with MOG antibody-negative ADS patients

The mean onset age of the 46 MOG antibody-positive patients with ADS (male: n = 21; female: n = 25) was 92.4 months (SD, 47.6 months). Thirty-five (35/46; 76.1%) MOG antibody-positive patients exhibited brain demyelination at the first presentation, and more than half (19/35, 54.3%) had encephalopathy; 9 of 11 patients without brain demyelination (81.8%) exhibited only ON. The phenotypes of the initial presentation were as follow: an ADEM-like event (41.3%), brain demyelination without encephalopathy with/without ON or TM (34.7%), isolated ON (19.6%), and other (4.4%, 1 patient with TM, 1 patient with TM+ON) (Figure. 2). The most common lesion locations in MOG antibody-positive patients during the follow-up period were the juxtacortical and subcortical white matter (57%), brainstem (46%), and optic pathway (43%), and the least involved site was the corpus callosum (13%). Eighteen (18/46, 39.1%) MOG antibody-positive patients experienced recurrence. A total of 14 of the 18 patients experienced the first relapse within 12 months, and 16 out of 18 (88.9%) had the first relapse within 2 years.

Compared with MOG antibody-negative patients, MOG antibody-positive patients more frequently had lesions in the juxtacortical or subcortical area (57% vs. 32%, p = 0.017) and in the optic pathway (43% vs. 21%, p = 0.018). Also, the mean EDSS

scores were significantly lower in MOG antibody-positive patients than in MOG antibody-negative patients ($p < 0.001$) (Table 2). Seven of the MOG antibody-negative patients had an EDSS score > 8, and none of the MOG antibody-positive patients had an EDSS scores > 5.

Figure 2.The initial presentation of ADS patients with MOG antibodies positive



ADS: aquired demyeinating syndrome, MOG: myelin oligodendrocyte glycoprotein, ON: optic neuritis, TM: transverse myelitis, ADEM: acute disseminated encephalomyelitis,

Table 2. MOG antibody-positive ADS vs MOG antibody-negative ADS patients.

	MOG antibody-positive N = 46	MOG antibody-negative N = 48	*p*-value
Mean age at onset, month (SD)	92.4 (47.6)	110.1 (48.9)	0.081
Sex (male:female)	21:25	18:30	0.530
Mean follow-up period, month (SD)	34.8 (36.4)	36.4 (41.9)	0.882
Recurrence, n/N (%)	18/46 (39)	17/48 (35)	0.710
Encephalopathy, n/N (%)	21/46 (46)	16/48 (33)	0.291
Involvement site, n/N (%)			
Cortex	10/46 (22)	8/47 (17)	0.565
Juxtacortical or subcortical WM	26/46 (57)	15/47 (32)	0.017
Periventricular WM	12/46 (26)	20/47 (43)	0.095
Deep WM	12/46 (26)	10/47 (21)	0.625
Corpus callosum	6/46 (13)	8/47 (17)	0.592
Basal ganglia	18/46 (39)	14/47 (30)	0.343
Thalamus,hypothalamus	16/46 (35)	11/47 (23)	0.227
Brainstem	21/46 (46)	18/47 (38)	0.472
Cerebellum	16/46 (35)	17/47 (36)	0.889
Optic pathway	20/46 (43)	10/47 (21)	0.018
Spine	14/46 (30)	20/47 (43)	0.225
Long	12/46 (26)	15/47 (32)	0.536
Short	2/46 (4)	5/47 (11)	0.250
CSF WBC (mean±SD, mm^3/dL)	32.4±44.2	16.0±39.1	0.088
Protein (mean±SD, mg/dL)	44.2±25.4	56.0±46.7	0.172
Glucose (mean±SD, mg/dL)	67.1±12.3	67.7±18.7	0.880
EDSS score (mean±SD)	0.3±0.8	2.7±3.4	〈0.001

ADS: aquired demyeinating syndrome, MOG: myelin oligodendrocyte glycoprotein, SD: standard deviation, WM: white matter, CSF: cerebrocpinal fluid, WBC: white blood cell

3. Acute disseminated encephalomyelitis

The mean onset age of the 29 patients with ADEM (male: n = 16; female: n = 13) was 68.0 months (SD, 44.1 months). Of the 29 patients with ADEM, 17 (58%) showed MOG antibody positivity. One patient was positive for both OCB in CSF and MOG antibodies. No patients were positive for AQP4 antibodies. One of the MOG-positive patients experienced a recurrence but was not treated for maintenance therapy. The most common lesion locations in patients with ADEM were the juxtacortical or subcortical white matter (59%), brainstem (59%), and basal ganglia (48%). Polyfocal demyelinaing lesions of brain are shown in both MOG positive and negative ADEM patients.(Figure 3) The mean EDSS score of the ADEM group was 1.5 (SD, 2.7).

MOG antibody-positive patients with ADEM had more frequent lesions of the juxtacortical or subcortical areas than MOG antibody-negative patients with ADEM ($p = 0.017$), and their mean EDSS score was also significantly lower ($p < 0.001$) (Table 3).

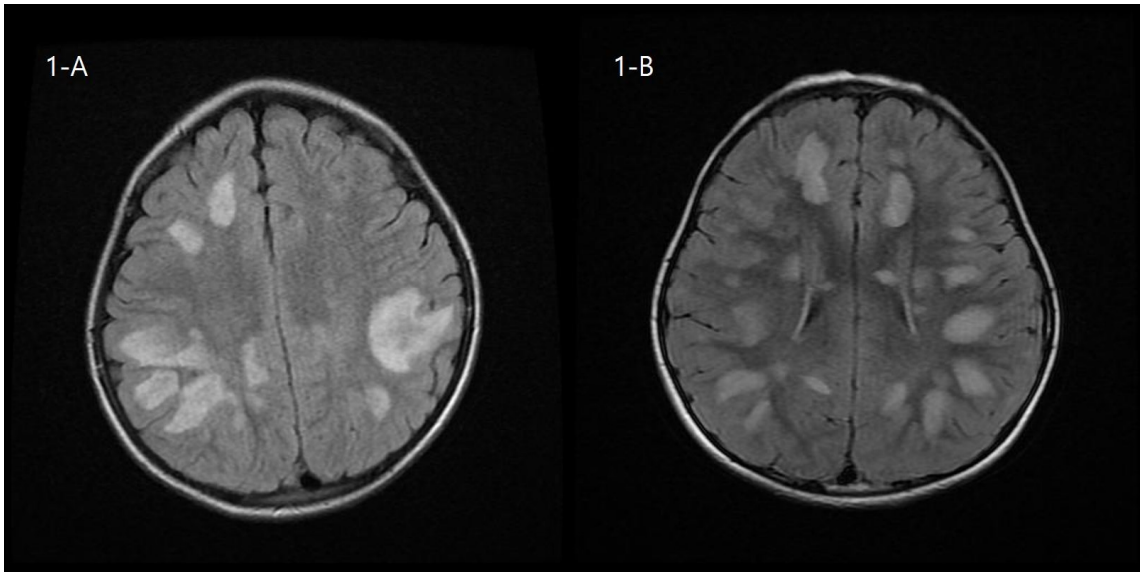


Figure 3. The T2 FLAIR show polyfocal lesions in brain MRI of ADEM patient 1 who showed MOG antibodies positive (A), similar multiple and large lesions are shown in patients 19 who is negative for MOG antibodies (B). FLAIR, fluid-attenuated inversion recovery; ADEM, acute disseminated encephalomyelitis; MRI, magnetic resonance imaging; MOG, myelin oligodendrocyte glycoprotein.

Table 3. MOG antibody-positive ADEM vs MOG antibody-negative ADEM patients.

	MOG antibody-positive N = 17	MOG antibody-negative N = 12	*p*-value
Mean age at onset, month (SD)	63.2 (33.8)	74.9 (56.6)	0.492
Sex (male:female)	10:7	6:6	0.638
Mean follow-up period, month (SD)	24.9 (29.7)	21.0 (14.8)	0.647
Recurrence, n/N (%)	1/17 (6)	0/12 (0)	0.414
Involvement site, n/N (%)			
Cortex	2/17 (12)	4/12 (33)	0.198
Juxtacortical or subcortical WM	13/17 (76)	4/12 (33)	0.029
Periventricular WM	4/17 (24)	4/12 (33)	0.561
Deep WM	7/17 (41)	5/12 (42)	1.000
Corpus callosum	2/17 (12)	3/12 (25)	0.622
Basal ganglia	8/17 (47)	6/12 (50)	0.343
Thalamus,hypothalamus	7/17 (41)	4/12 (33)	0.717
Brainstem	8/17 (47)	9/12 (75)	0.251
Cerebellum	7/17 (41)	3/12 (33)	0.449
Optic pathway	2/17 (12)	0/12 (0)	0.498
Spine	6/17 (35)	3/12 (25)	0.694
Long	4/17 (24)	3/12 (25)	1.000
Short	2/17 (12)	0/12 (0)	0.498
CSF WBC(mean±SD, mm^3/dL)	19.3±28.5	36.0±65.3	0.424
Protein (mean±SD, mg/dL)	54.5±32.6	73.4±63.7	0.367
Glucose (mean±SD, mg/dL)	67.1±12.9	72.9±21.1	0.395
EDSS score (mean±SD)	0.4±1.0	3.2±3.6	0.025

ADEM: acute disseminated encephalomyelitis, MOG: myelin oligodendrocyte glycoprotein, SD: standard deviation, WM: white matter, CSF: cerebrocpinal fluid, WBC: white blood cell

4. Multiple sclerosis

The mean onset age of the 12 patients (male: n = 8; female: n = 4) diagnosed with MS was 103.4 months (SD, 38.1 months), and 5 of the 12 patients showed MOG antibody positivity. One patient diagnosed with MS was positive for OCB in CSF and negative for the MOG antibody. No patients were positive for AQP 4 antibodies. All patients diagnosed with MS experienced a recurrence. Nine patients (4 patients with MOG antibodies positive, 5 patients with MOG antibodies negative) were treated using maintenance therapy, of which the most common was interferon beta (22mcg 3 times per week) treatment {7 patients, (MOG antibodies positive: 2 patients, 5 MOG antibodies negative: 5 patients)}. These 7 patients show no relapse after interferon beta administration. One of the other two took azathioprine (2mg/kg per day) and prednisolone (1mg/kg per day) after the 3rd attack, but changed the drug to mycophenolate mofetil (20mg/kg) and prednisolone (1mg/kg) after the fourth attack until now. The other, after the third attack, maintained only the prednisolone (1mg/kg, every other day) for 3 years and stopped without relapse. The mean EDSS score of the MS group was 1.0 (SD 1.7). The most common lesion locations in patients with MS were the juxtacortical or subcortical white matter (80%) and periventricular area (80%) (Figure 4,5,6).

MOG antibody-positive patients had lesions in cortex (p =

0.010) and brainstem (p = 0.010) more frequently than MOG antibody-negative patients. In addition, MOG antibody-positive patients tended to be younger than MOG antibody-negative patients (mean: 86.9 months vs. 115.2 months), and to less commonly have periventricular lesions (60% vs 100%), but these differences were not significantly different (Table 4).

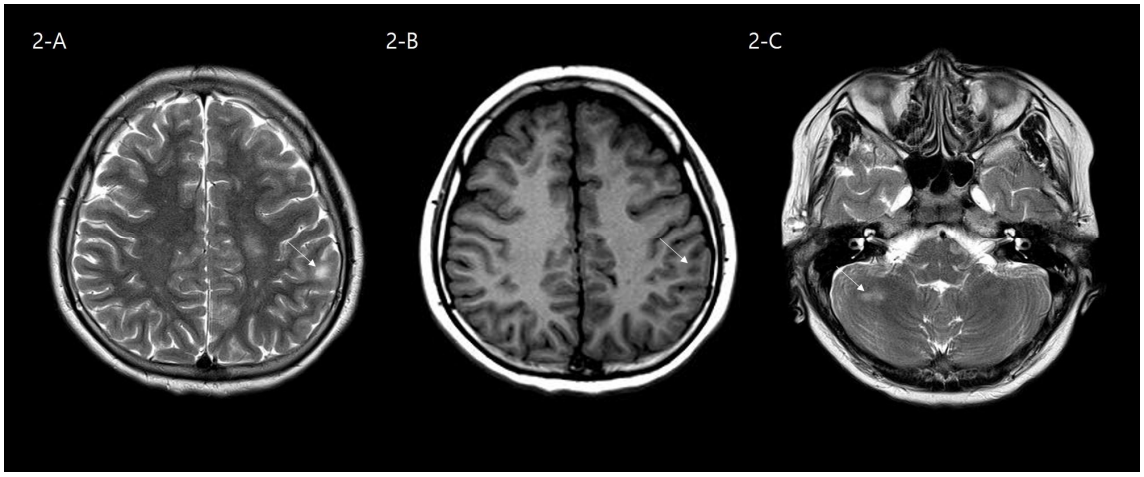


Figure 4. Brain MRI of patient 33 diagnosed with MS (oligoclonal bands in cerebrospinal fluid positive). Juxstacortical lesion with high signal intensity is shown on The T2 weighted image (A) and have low signal intensity on The T1 weighted images (B). Lesion in cerebellar white matter on The T2 weighted images (C). MRI, magnetic resonance imaging; MS, multiple scleros

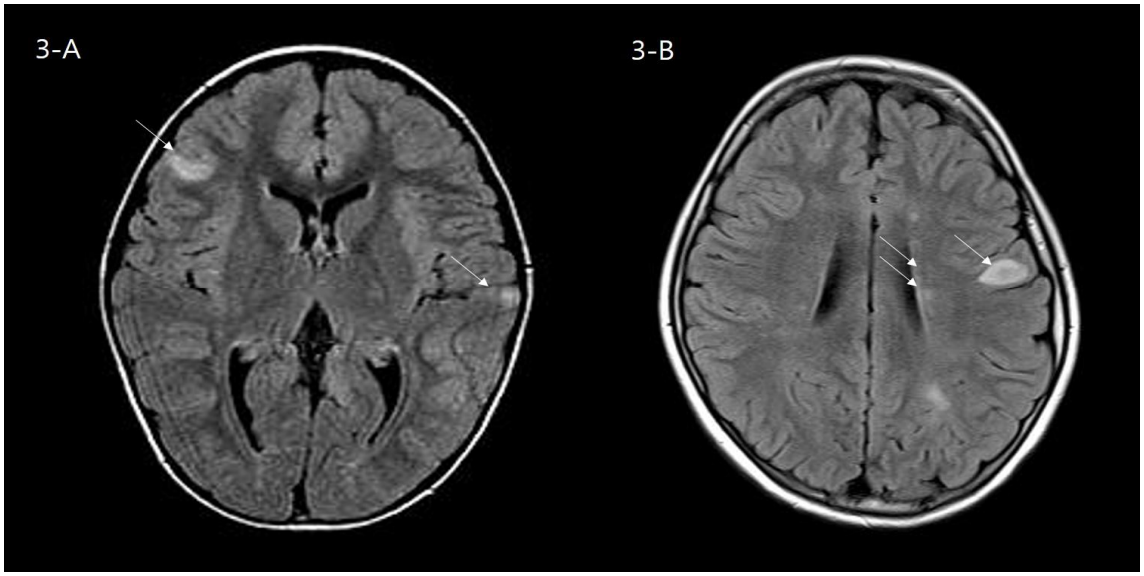


Figure 5. Brain MRI of patient 35 diagnosed with MS (MOG antibodies positive). Juxstacortical or subcortical lesions including cortex are shown on The T2 FLAIR (A). Periventricular and subcortical lesions are shown on The T2 FLAIR (B). MRI, magnetic resonance imaging; MOG, myelin oligodendrocyte glycoprotein; FLAIR, fluid-attenuated inversion recovery

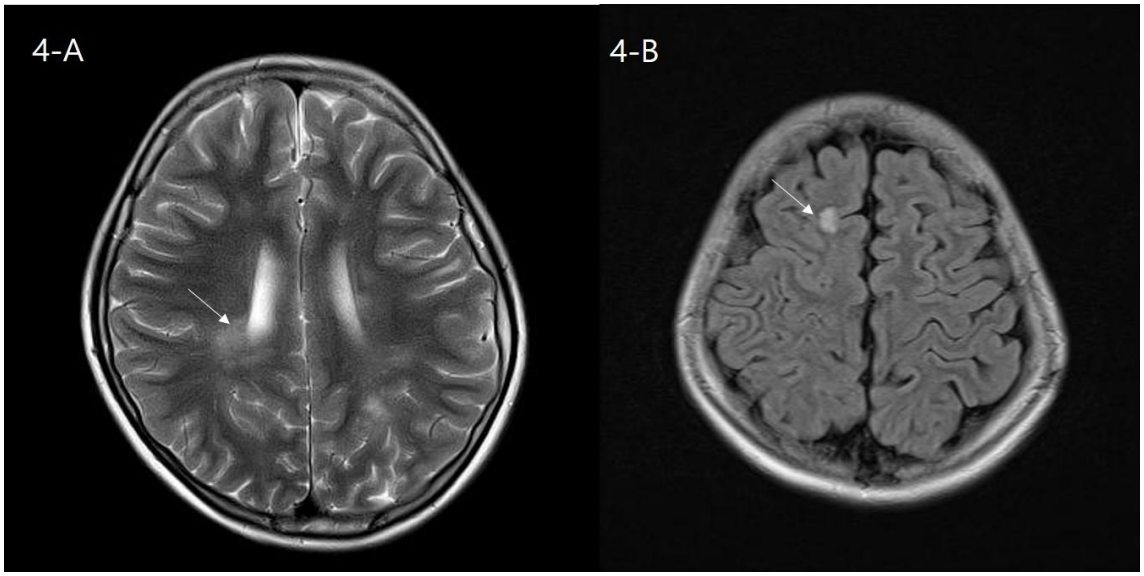


Figure 6. Brain MRI of patient 34 diagnosed with MS (MOG antibodies positive). Periventricular lesions is shown on The T2 weighted image (A). The T2 FLAIR show juxtacortical lesion (B). MRI, magnetic resonance imaging; MOG, myelin oligodendrocyte glycoprotein; FLAIR, fluid-attenuated inversion recovery

Table 4. MOG antibody-positive MS vs MOG antibody-negative MS patients

	MOG antibody-positive N = 5	MOG antibody-negative N = 7	*p*-value
Mean age at onset, month (SD)	86.9 (39.0)	115.2 (35.3)	0.217
Sex (male:female)	3:2	5:2	1.000
Mean follow-up period, month (SD)	96.7 (52.7)	97.0 (67.3)	0.994
Recurrence, n/N (%)	5/5 (100)	7/7 (100)	
Encephalopathy, n/N (%)	2/5 (40)	3/7 (43)	1.000
Involvement site, n/N (%)			
Cortex	4/5 (80)	0/7 (0)	0.010
Juxtacortical or subcortical WM	4/5 (80)	6/7 (86)	1.000
Periventricular WM	3/5 (60)	7/7 (100)	0.152
Deep WM	4/5 (80)	2/7 (29)	0.242
Corpus callosum	2/5 (40)	4/7 (57)	1.000
Basal ganglia	4/5 (80)	3/7 (43)	0.293
Thalamus, hypothalamus	3/5 (60)	3/7 (43)	1.000
Brainstem	4/5 (80)	0/7 (0)	0.010
Cerebellum	4/5 (80)	4/7 (57)	0.576
Optic pathway	1/5 (20)	2/7 (29)	1.000
Spine	0/5 (0)	4/7 (57)	0.081
Long	0/5 (0)	1/7 (14)	1.000
Short	0/5 (0)	3/7 (43)	0.205
CSF WBC (mean±SD, mm^3/dL)	11.3±18.6	4.7±10.0	0.458
Protein (mean±SD, mg/dL)	38.4±8.6	35.7±20.6	0.811
Glucose (mean±SD, mg/dL)	61.0±2.8	55.9±24.9	0.702
EDSS score (mean±SD)	0.4±0.5	1.5±2.3	0.319

MS: multiple sclerosis, MOG: myelin oligodendrocyte glycoprotein, SD: standard deviation, WM: white matter, CSF: cerebrocpinal fluid, WBC: white blood cell

5. Neuromyelitis optica spectrum disorder

The mean onset age of the 12 patients diagnosed with NMOSD (male: n = 2; female: n = 10) was 108.8 months (SD, 46.4 months), and 6 of these 12 showed MOG antibody positivity. There were five AQP4 antibody-positive patients, none of whom were positive for MOG antibodies. No patients were positive for CSF OCB. Nine out of the twelve patients experienced a recurrence. Of these, 6 patients (4 patients with MOG antibodies positive, 2 patients with MOG antibodies negative) were treated using maintenance therapy. In cases of the 4 MOG positive patients with maintenance therapy, one patient received azathioprine (1mg/kg per day) and prednisolone (1mg/kg per day) after third attack for 3 years and discontinued medication without relapse. One patient received azathioprine (2mg/kg per day) and prednisolone (0.5mg/kg every other day) after second attack, then prednisolone was maintained for 6 months and azathioprine for 2 years without relpase. one patient received azathioprine (1mg/kg per day) after third attack, but azathioprine was changed to mycophenolic acid (20mg/kg per day) after fourth attack. This patient has not been to the hospital anymore since mycophenolic acid administration. The other one started using mycophenolic acid (40mg/kg per day) and prednisolone (0.5mg every other day) together after the second attack, then prednisolone was maintained for 2 years and is mycophenolic acid still being administered without relapse. In cases of the 2 MOG negative patients (all: aquaporin 4 antibodies positive) with

maintenance therapy, one patient received mycophenolic acid (10mg/kg per day) after second attack, but relapse continued, so mycophenolic acid (40mg/kg/day) was increased and prednisolone (1mg/kg per day) was added. This patient had no further relapse for 6 months. The other one received mycophenolic acid (10mg/kg per day) and azathioprine (2mg/kg per day) after second attack for 3 years until now without replase. The mean EDSS score of the NMOSD group was 1.7 (SD, 3.2). The most common lesion locations in patients with NMOSD were the spinal cord (92%), optic pathway (83%), and periventricular area (58%).(Figure 7,8,9)

MOG antibody-positive patients had a significantly lower number of CSF white blood cells than MOG antibody-negative patients (p = 0.036). MOG antibody-positive patients frequently had lesions in the cortex (33%), juxtacortical or subcortical white matter (50%), and basal ganglia (50%). In contrast, MOG antibody-negative patients showed no lesions in these areas. In addition, MOG antibody-positive patients were younger and had a better prognosis than MOG antibody-negative patients, but these differences were not significant (Table 5).

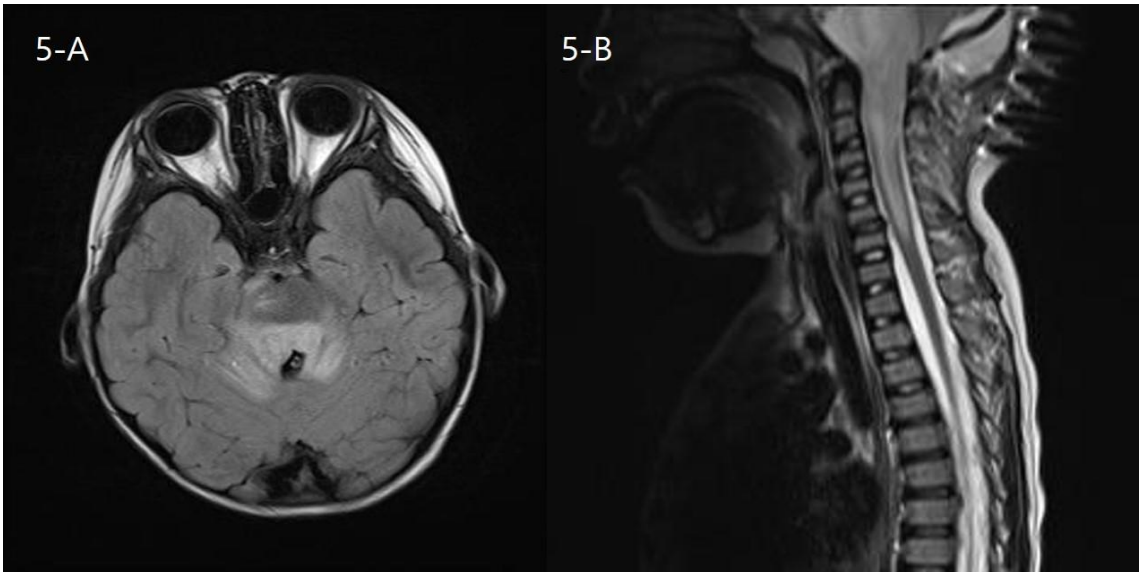


Figure 7. Brain and spine MRI of patient 45 diagnosed with NMOSD (Aquaporin 4 antibodies positive). The T2 high signal intensity lesion of brain stem and bilateral cerebellar peduncle is shown on T2 FLAIR (including periaqueductal and 4th ventricle area) (A). The high signal lesion from brain stem to C6 level is shown on The T2 weighted image (B). MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica disorder; FLAIR, fluid-attenuated inversion recovery

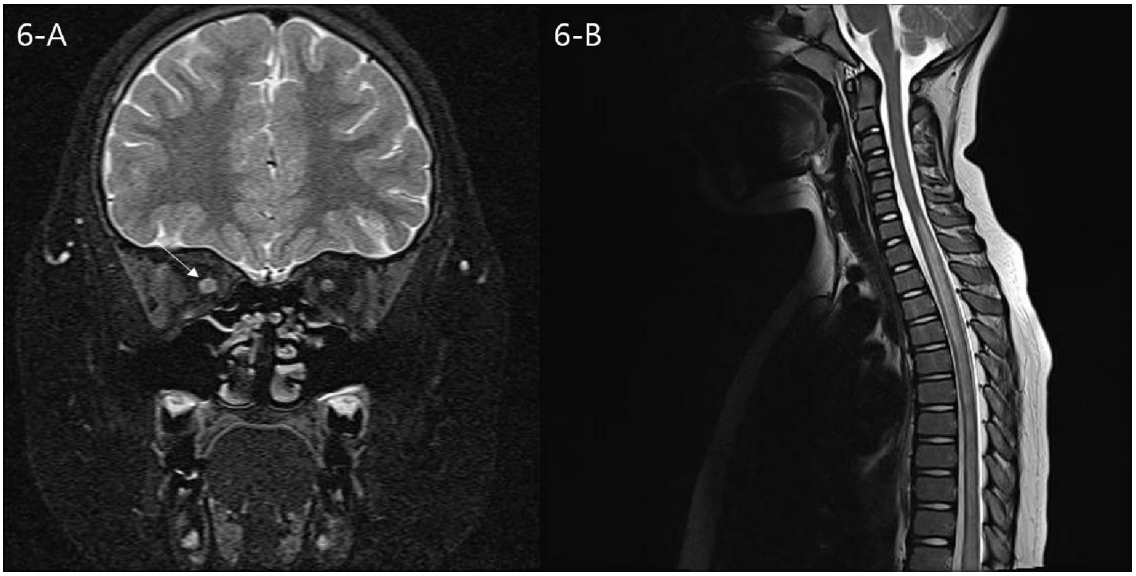


Figure 8. Orbit and spine MRI of patient 47 diagnosed with (MOG antibodies positive). The T2 high signal intensity lesion and swelling of right optic nerve in shown on The T2 weighted image (A). Diffuse spinal cord lesion with high signal intensity is shown on The T2 weighted image (B). MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; MOG, myelin oligodendrocyte glycoprotein

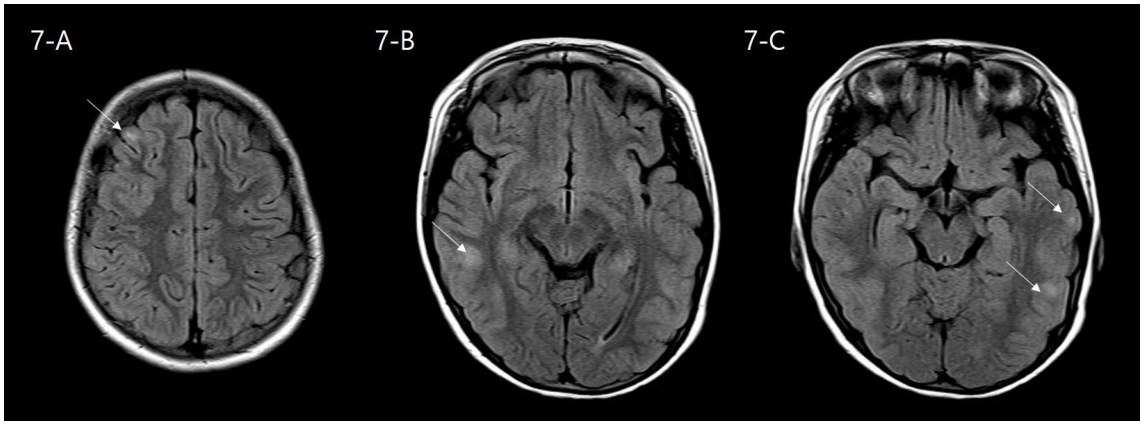


Figure 9. Brain MRI of patient 47 diagnosed with NMOSD (MOG antibodies positive) Multiple juxtacortical or subcortical lesions are shown on T2 FLAIR (A,B,C).MRI, magnetic resonance imaging; MOG, myelin oligodendrocyte glycoprotein; FLAIR, fluid-attenuated inversion recovery

Table 5. MOG antibody-positive NMOSD vs MOG antibody-negative NMOSD patients

	MOG antibody-positive N = 6	MOG antibody-negative N = 6	*p*-value
Mean age at onset, month (SD)	84.4 (29.8)	133.2 (49.1)	0.064
Sex (male:female)	1:5	1:5	1.000
Mean follow-up period, month (SD)	28.6 (19.5)	35.8 (30.5)	0.636
Recurrence, n/N (%)	5/6 (39)	4/6 (35)	1.000
Encephalopathy, n/N (%)	0/6 (0)	0/6 (0)	
Aquaporin 4 antibody	0/6	5/6	0.015
Involvement site, n/N (%)			
Cortex	2/6 (33)	0/6 (0)	0.455
Juxtacortical or subcortical WM	3/6 (50)	0/6 (0)	0.182
Periventricular WM	3/6 (50)	4/6 (66)	1.000
Deep WM	0/6 (0)	0/6 (0)	
Corpus callosum	1/6 (17)	0/6 (0)	1.000
Basal ganglia	3/6 (50)	0/6 (0)	0.182
Thalamus,hypothalamus	1/6 (17)	0/6 (0)	1.000
Brainstem	3/6 (50)	3/6 (50)	1.000
Cerebellum	3/6 (50)	3/6 (50)	1.000
Optic pathway	6/6 (100)	4/6 (67)	1.000
Spine	6/6 (100)	5/6 (83)	1.000
Long	6/6 (100)	4/6 (66)	0.455
Short	0/6 (0)	1/6 (17)	1.000
CSF WBC (mean±SD, mm^3/dL)	69.2±56.8	3.5±5.7	0.036
Protein (mean±SD, mg/dL)	38.3±29.2	96.5±73.9	0.216
Glucose (mean±SD, mg/dL)	69.5±12.4	58.5±10.0	0.179
EDSS score (mean±SD)	0.2±0.4	3.1±4.1	0.157

NMOSD: neuromyelitis optica spectrum disorder, MOG: myelin oligodendrocyte glycoprotein, SD: standard deviation, WM: white matter, CSF: cerebrocpinal fluid, WBC: white blood cell

6. Unclassified

The mean onset age of the 12 patients (male: n = 2; female: n = 10) diagnosed with unclassified was 117.6 months (SD, 40.6 months), and 7 out of 12 showed MOG antibody positivity. None of these patients were positive for the AQP4 antibody or CSF OCB. All patients experienced a recurrence. Seven patients were treated using maintenance therapy (5 patients with MOG antibodies positive, 2 patients with MOG antibodies negative). In cases of the 5 MOG positive patients with maintenance therapy, Two patients were given prednisolone (one: 1mg/kg per day, the other one 0.5mg/kg per day) for 6 months without relapse. one patient was treated with interferon beta (22mcg/kg per 3 times /week) after second attack for 3 years, but she experienced relapse and interferon was changed to azathioprine (1mg/kg per day). Then, she showed additional relpase and has not been to the hospital anymore. One patient was given azathioprine (1mg/kg per day) after first attack and regimen was changed to mycophenolic acid after second attack. Then, the medication continued for 3 years without relapse. The last one took azathioprine (1mg/kg per day) after second attack for 2 years. he experienced one additional attack 6 months after maintenance therapy, but the dose of azathioprine was not changed and prednisolone (1mg/kg per day) was added only for 3 months after third attack. In cases of the 2 MOG negative patients with maintenance therapy, one patient was treated azathiopirne (1mg/kg per day) after third attack,

the dose was escalated to 2mg/kg per day after fourth attack. After fifth attack, the regimen was changed to mycophenolic acid (20mg/kg per day. The dose was escalated to 30mg/kg per day after sixth attack and was maintained (for 2.5 years) without additional relapse. The other one was treated with azathioprine (1mg/kg per day) after first attack for 3 years and medication was changed to mycophenolic acid (10mg/kg per day) was continued until last visit (for one year). The mean EDSS score of the unclassified group was 0.5 (SD, 1.2). The most common lesion locations in patients with unclassified were the juxtacortical or subcortical white matter (45%), thalamus and hypothalamus (45%), brainstem (45%), and optic pathway (45%). MOG antibody-positive patients showed less frequent lesions of the periventricular area than the MOG antibody-negative patients (p = 0.024; Table 6).

Table 6. MOG antibody-positive unclassified vs MOG antibody-negative unclassified patients

	MOG antibody-positive N = 7	MOG antibody-negative N = 5	*p*-value
Mean age at onset, month (SD)	124.8 (47.7)	107.5 (30.0)	0.493
Sex (male:female)	1:6	1:4	1.000
Mean follow-up period, month (SD)	34.8 (36.4)	36.4 (41.9)	0.461
Recurrence, n/N (%)	7/7 (100)	5/5 (100)	
Encephalopathy, n/N (%)	2/7 (29)	1/5 (20)	1.000
Involvement site, n/N (%)			
Cortex	2/7 (29)	2/4 (50)	0.576
Juxtacortical or subcortical WM	3/7 (43)	2/4 (50)	1.000
Periventricular WM	0/7 (0)	3/4 (75)	0.024
Deep WM	0/7 (0)	1/4 (25)	0.364
Corpus callosum	0/7 (0)	0/4 (0)	
Basal ganglia	2/7 (29)	1/4 (25)	1.000
Thalamus,hypothalamus	4/7 (57)	1/4 (25)	0.545
Brainstem	4/7 (57)	1/4 (25)	0.545
Cerebellum	2/7 (29)	2/4 (50)	0.889
Optic pathway	3/7 (43)	2/4 (50)	1.000
Spine	1/7 (14)	2/4 (50)	0.491
Long	1/7 (14)	2/4 (50)	0.491
Short	0/7 (0)	0/4 (0)	
CSF WBC (mean±SD, mm^3/dL)	47.6±54.1	15.5±12.2	0.261
Protein (mean±SD, mg/dL)	42.6±7.5	36.8±7.6	0.286
Glucose (mean±SD, mg/dL)	68.8±15.4	70.5±12.2	0.862
EDSS score (mean±SD)	0.4±1.1	0.8±1.5	0.695

MOG: myelin oligodendrocyte glycoprotein, SD: standard deviation, WM: white matter, CSF: cerebrocpinal fluid, WBC: white blood cell

7. CIS (ON, TM, and other CISs)

The other CISs included 16 participants (male: n = 5; female: n = 11) and the mean onset age was 126.5 months (SD, 46.8 months). Four patients (25%) were positive for MOG antibodies. No patients in the other CIS group were positive for AQP4 antibodies or CSF OCB. The mean EDSS score of the CIS group was 1.6 (SD, 2.8). The most common lesion locations were the brainstem (44%), juxtacortical or subcortical white matter (33%), and basal ganglia (33%). There were no significant differences in age of onset, sex, follow-up period, or lesion location between MOG antibody-positive and negative patients (Table 7).

The mean age of onset of the 8 patients with ON (male: n = 4; female: n = 4) was 111.9 months (SD, 48.3 months). Of these 8, 7 patients (78%) was found to be positive for MOG antibodies. One (MOG antibody-positive) patients with ON experienced relapses and was treated with mycophenolic acid. Only one patients of the six patients in whom the EDSS was applied had a score of 1; all others had no disability.

The mean age of the five patients with isolated TM (male: n = 2; female: n = 3) was 142.3 months (SD, 36.8) and all were monophasic. Patients showed negative results in MOG antibodies, AQP4 antibodies, and CSF OCB. All patients had lesions of more than three of the vertebral segments. Prednisone was used to treat the four

patients for whom these data were available, and plasmapheresis was used in two patients and intravenous immunoglobulin in one patient. Patients′ prognosis was varied; two patients fully recovered and three showed an EDSS score of more than 8.5.

Table 7. MOG antibody-positive other CIS vs MOG antibody-negative other CIS patients

	MOG antibody-positive N = 4	MOG antibody-negative N = 12	*p*-value
Mean age at onset, month (SD)	152.8 (43.9)	117.7 (46.1)	0.203
Sex (male:female)	2:2	3:9	0.547
Mean follow-up period, month (SD)	23.4 (17.2)	16.7 (18.1)	0.525
Encephalopathy, n/N (%)	0/4 (0)	0/12 (0)	
Involvement site, n/N (%)			
Cortex	0/4 (0)	1/12 (8)	1.000
Juxtacortical or subcortical WM	2/4 (50)	3/12 (25)	0.547
Periventricular WM	1/4 (25)	3/12 (25)	1.000
Deep WM	0/4 (0)	2/12 (17)	1.000
Corpus callosum	0/4 (0)	1/12 (8)	1.000
Basal ganglia	1/4 (25)	4/12 (33)	1.000
Thalamus, hypothalamus	1/4 (25)	3/12 (25)	1.000
Brainstem	2/4 (50)	5/12 (42)	1.000
Cerebellum	0/4 (0)	5/12 (42)	0.245
Optic pathway	1/4 (25)	1/12 (8)	0.450
Spine	1/4 (25)	1/12 (8)	0.450
Long	1/4 (25)	0/12 (0)	0.250
Short	0/4 (0)	1/12 (8)	1.000
CSF WBC (mean±SD, mm^3/dL)	63.0±1.0	66.8±1.2	0.249
Protein (mean±SD, mg/dL)	32.0±18.4	38.0±14.2	0.615
Glucose (mean±SD, mg/dL)	60.0	67.9±10.2	0.484
EDSS score (mean±SD)	0.0±0.0	2.1±3.1	0.277

CIS: clinically isolated syndrome, MOG: myelin oligodendrocyte glycoprotein, SD: standard deviation, WM: white matter, CSF: cerebrocpinal fluid, WBC: white blood cell

Discussion

Our study used the different classification such as other CISs and unclassified form with relapse with International Pediatric Multiple Sclerosis Study Group 2013 criteria. We defined other CISs defined as all CISs except isolated ON and isolated TM. Previous studies showed that children with Isolated TM or Isolated ON are less likely to be diagnosed with MS in subsequent events[13,14]. Therefore, we subdivided CIS into other CISs and isolatd TM and isolated ON to emphasize the fact that other CISs is a group with brain demyelination without encephalopathy. We defined unclassified form with relapse as multiphasic demyelinating form that is neither satisfied with 2015 NMOSD criteria nor with MS criteria of International Pediatric Multiple Sclerosis Study Group 2013 because we thought that these patients have different etiology with patients with diagnosed with MS or NMOSD.

In this study, we identified the presence of three biomarkers in children with ADS to determine their potential for diagnosing pediatric ADS in Korea. OCB was positive in two out of 45 (4%) pediatric patients (including 1 patient with MS and 1 patient with ADEM). This suggests that OCB has a very low detection rate in Korean children with ADS. The low detection rate of OCB is probably due to the low number of patients with MS in Korean pediatric patients with ADS. Previous reports have estimated the proportion of MS diagnosis

after the first demyelination event in children ADS to be 15 to 57%.[13-16] The difference between our result and earlier report may be geographic variation or select bias of this study.[17,18] However, the prevalence of MS in Korean children with ADS is not well known. Therefore, a prospective and multi-center study is needed to more accurately determine the proportion of MS in Korean children with ADS. The second possibility is that the patients were misdiagnosed with MS. In this study, 5 patients diagnosed with MS were positive for MOG antibodies. One previous study reported that younger children with MS are more likely to have an ADEM-like first attack, can have large, ill-defined lesions early in the disease course, and are less likely to have CSF OCB than adolescent-onset patients with MS.[3] These features are often seen in patients under 12 years of age, similar to the clinical characteristics in MOG antibody-positive ADEM patients. One study has also suggested that childhood MOG antibody-positive patients may be diagnosed with non-typical MS.[19] For these reasons, we concluded that the detection rate of OCB in Korean pediatric patients with ADS is low due to the small proportion of patients with typical MS in Korean children with ADS. Therefore, OCB is limited in its ability to diagnose children with ADS due to its low detection rate although it could be supportive for MS diagnosis, according to the McDonald criteria of 2017.[4] AQP4 antibodies have a main role in the pathological mechanisms underlying NMOSD, according to the 2015 NMOSD criteria, and are crucial for the

diagnosis of NMOSD.[5] In this study, 5 of the 75 patients were positive for AQP4 antibodies; 3 of these had long TM (〉 three segment vertebrae) with ON and brain demyelination , 1 patient had long TM and brain demyelination, 1 patient had isolated ON. In addition, brain lesion of AQP4 positive NMOSD located in periventricular white matter, cerebellum, midbrain around CSF space. Therefore, the phenotype of the patients identified with AQP4 antibodies in this study are consistent with the typical appearance of NMOSD.[20-23] AQP4 antibody-positive patients with NMOSD accounted for 7% of the entire ADS patient sample in this study. Our results are similar to those of a study conducted in the United States, in which NMOSD accounted for 6% of patients with ADS aged between 12 and 18 years.[24] We found that the detection rates of OCB and AQP4 antibodies among pediatric patients with ADS in Korea were less than 10% each. This suggests that the proportion of typical MS and AQP4-positive NMOSD cases in children with ADS is low. Therefore, it is important to selectively perform an OCB or assess AQP4 antibodies testing by analyzing clinical symptoms and neuroimaging.

MOG antibody-positive patients represented 48% of our cohort. In past studies, the MOG antibody positivity rates have ranged between 18% and 42%.[25-27] Although there are some differences between each study, it seems clear that the MOG antibody rate in children with ADS is higher than that of OCB or AQP4 antibodies. According to previous literature, the positivity rate is commonly detected in

children with ADEM, ON, and AQP4-negative NMOSD.[9,10,25-28] These are similar results to that of the present study. However, we also found the presence of MOG antibodies in children diagnosed with MS, unclassified form with relapse. Currently, it is still unclear whether MOG antibodies can be positive for MS patients. Some studies have confirmed that the MOG antibody is rarely found in patients with MS.[9,26] In contrast, one study found that 33% of the MOG antibody-positive adult patients fulfilled the McDonald criteria,[29] and some studies have found MOG antibody positivity in children diagnosed with MS.[25,30] Given that some patients diagnosed with MS were positive for MOG antibodies in this study, we believe that MOG antibodies are not identified in MS patients, but that some MOG-positive patients can meet MS criteria. MOG antibody-associated disease and MS are different diseases with different underlying pathophysiological mechanisms, prognoses neuroimaging and outcome, and we need to be distinguished for these diseases.[28,31] We classified patients with no definite diagnosis as the unclassified form. In pediatric patients with ADS who experience relapse, it is often challenging to make an adequate diagnosis as some patients do not clearly fulfill the diagnostic criteria of MS or NMOSD. In our study, 12 of 35 (34%) patients with relapse had no clear diagnosis. We found that 58% (7/12) of these patients were positive for the MOG antibody. This finding is of great significance as it suggests that MOG antibody testing could aid the diagnosis of children who are unable to be

accurately diagnosed by clinical features and neuroimaging findings alone. We recommend the MOG antibody test for all pediatric patients with ADS in Korea except for those with monophasic TM, especially prior to a diagnosis of MS and in patients without a clear diagnosis.

We also investigated the characteristics of MOG antibody-positive patients. There were no significant demographic differences between the MOG antibody-positive patients and MOG antibody-negative patients in this study. However, the mean EDSS score was lower in the MOG-positive group than in the MOG-negative group. This result is similar to those previously reported.[9] The difference in the distribution of lesions between the two groups was small, except for in the juxtacortical or subcortical area and optic pathway. This could be because the lesion sites of MOG antibody-positive patients were very diverse rather than concentrated in a specific area in this study. MOG antibody-positive patients frequently had lesions of the juxtacortical white matter, brainstem, basal ganglia, and optic pathway. However, lesions in other areas were found in more than 20% of patients, such as in the cortex, periventricular area, deep white matter, thalamus and hypothalamus, cerebellum, and spinal cord. A previous study reported that lesions of the brainstem and deep gray matter were frequently found in MOG antibody-positive patients with ADS and also found lesions in other areas such as subcortical white matter and

periventricular in pediatric patients.[32] This suggests that MOG antibody-positive children have a variable phenotype and initial presentation due to diverse involvement sites. Our result showed that MOG antibodies could be found in all type ADS except isolated TM although there is a difference in detection rate according to phenotype. Considering that the MOG antibody-negative patient group was a collection of various diagnostic groups, including MS and NMOSD, it was difficult to identify any further clinical significance. Thus, we conducted a subgroup analysis.

In MOG antibody-positive ADEM patients, lesions of the juxtacortical white matter were more common than in MOG antibody-negative ADEM patients, but there was no significant difference in the other areas. In addition, the mean EDSS score of the MOG antibody-positive ADEM patients was lower than that of the MOG antibody-negative ADEM patients; however, this difference was the result of two MOG antibody-negative ADEM patients who had an EDSS score of 9.5 or higher. Therefore, we could not confidently determine whether the two groups were significantly different disease. In previous work , MOG antibody-positive ADEM patients and MOG antibody-negative ADEM patients did not show significant differences in demographic and clinical features except outcome and the MOG antibody negative group included some patients with particularly poor prognosis.[33] Thus, we suggest that the difference of prognosis between two groups was due to the inclusion of patients with a different

etiology in the MOG antibody-negative ADEM group. In patients diagnosed with MS, we found that MOG antibody-positive patients were more likely to have cortex and brainstem lesions than the MOG antibody-negative patients. Lesions of the cortex and brainstem are commonly found in patients with typical MS.[34,35] Especially, cortical lesions are known to be specific to an MS diagnosis.[34,36] But, we found that cortical lesions were found in MOG antibody-positive ADS children, this finding was confirmed in past study.[32] This suggests that we should rule out MOG antibody positive diseases before diagnosing patients with MS if pediatric ADS patients have a cortical lesion. For patients diagnosed with NMSOD, the MOG antibody-negative and MOG antibody-positive groups showed distinct differences. In the MOG antibody-negative group, AQP4 antibodies were identified in 5 out of 6 patients. These results are similar to previous results that showed that MOG antibodies are frequently detected in patients with AQP4-negative NMOSD.[10,37] Lesions in MOG antibody-positive NMOSD patients were mainly concentrated around CSF spaces, such as the periventricular area, brainstem, and cerebellum, in which AQP4 levels are high. On the other hand, MOG antibody-positive patients showed lesions in cortex, juxtacortical or subcortical white matter, and basal ganglia, as well as in the brainstem and cerebellum. This difference in the distribution of lesions confirms those reported in a previous study, and may help differentiate between APQ4-positive patients with NMOSD and

MOG-associated diseases.[38] In addition, the two groups differed in prognosis and age of onset, although these differences were not statistically significant, which could be due to the small cohort. Thus, we suggest that the two groups had a distinct biomarker status, onset age, involvement site, and prognosis. In the unclassified and CIS groups, no distinct difference in demographic, neuroimaging data, prognoses and CSF characteristics were found between the MOG antibody-positive group and the MOG antibody-negative group. This is likely due to the fact that the unclassified and CIS groups included various patient groups that did not have consistent characteristics. Addionally, we tried to investigate the difference of treatment response between MOG positve patients with MOG negative patients in subgroups. But, This study was not a controlled study, the number of patients undergoing maintenance therapy was small, the starting time of maintenance therapy varied, and the regimen administered to the patient was inconsistent. Therefore, it is impossible to verify the the difference of treatment effect.

This study has some limitations that should be noted. First, the study was conducted at a single tertiary hospital. Thus, our cohort cannot represent all children with ADS in Korea, and the referral bias might have also influenced the biomarker-positive rate. Second, this was not a longitudinal study and so the association of the patients′ prognosis with temporal changes in MOG antibodies could not be investigated. Third, this study was not a controlled study, the number

of patients undergoing maintenance therapy was small, the starting time of maintenance therapy varied, and the regimen administered to the patient was inconsistent. Therefore, it was not impossible to exclude a treatment effect, and further prospective studies are needed to determine the factors associated with relapses.

Conclusion

The MOG antibody (48% positivity rate) is a more relevant biomarker than OCB in CSF and AQP4 antibody in Korean children with ADS. It is useful for the diagnosis of relapsing ADS without definite diagnosis and should be performed before an MS diagnosis. Frequent involvement of the cortex and subcortical white matter in MOG antibody-positive patients may lead to a misdiagnosis of MS and could help differentiate MOG antibody-associated disease from APQ4-positive NMOSD.

References

1. Hintzen RQ, Dale RC, Neuteboom RF, Mar S, Banwell B. Pediatric acquired CNS demyelinating syndromes: Features associated with multiple sclerosis. Neurology 2016;87:S67-73.

2. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler 2013;19:1261-7.

3. Chabas D, Ness J, Belman A, et al. Younger children with MS have a distinct CSF inflammatory profile at disease onset. Neurology 2010;74:399-405.

4. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.

5. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89.

6. Wells E, Hacohen Y, Waldman A, et al. Neuroimmune disorders of the central nervous system in children in the molecular era. Nat Rev Neurol 2018;14:433-45.

7. Baumann M, Hennes EM, Schanda K, et al. Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): Extending the spectrum of MOG antibody positive diseases. Mult Scler 2016;22:1821-9.

8. Di Pauli F, Reindl M, Berger T. New clinical implications of anti-myelin oligodendrocyte glycoprotein antibodies in children with CNS demyelinating diseases. Mult Scler Relat Disord 2018;22:35-7.

9. Hacohen Y, Absoud M, Deiva K, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. Neurol Neuroimmunol Neuroinflamm 2015;2:e81.

10. Rostasy K, Mader S, Hennes EM, et al. Persisting myelin oligodendrocyte glycoprotein antibodies in aquaporin-4 antibody negative pediatric neuromyelitis optica. Mult Scler 2013;19:1052-9.

11. Rostasy K, Mader S, Schanda K, et al. Anti-myelin oligodendrocyte glycoprotein antibodies in pediatric patients with optic neuritis. Arch Neurol 2012;69:752-6.

12. Kim Y, Hyun JW, Woodhall MR, et al. Refining cell-based assay to detect MOG-IgG in patients with central nervous system

inflammatory diseases. Mult Scler Relat Disord 2020;40:101939.

13. Alper G, Petropoulou KA, Fitz CR, Kim Y. Idiopathic acute transverse myelitis in children: an analysis and discussion of MRI findings. Mult Scler 2011;17:74-80.

14. Wilejto M, Shroff M, Buncic JR, Kennedy J, Goia C, Banwell B. The clinical features, MRI findings, and outcome of optic neuritis in children. Neurology 2006;67:258-62.

15. Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. Lancet Neurol 2011;10:436-45.

16. Mikaeloff Y, Suissa S, Vallee L, et al. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. J Pediatr 2004;144:246-52.

17. Neuteboom RF, Boon M, Catsman Berrevoets CE, et al. Prognostic factors after a first attack of inflammatory CNS demyelination in children. Neurology 2008;71:967-73.

18. Tantsis EM, Prelog K, Brilot F, Dale RC. Risk of multiple sclerosis after a first demyelinating syndrome in an Australian Paediatric cohort: clinical, radiological features and application of the McDonald 2010 MRI criteria. Mult Scler 2013;19:1749-59.

19. Collaborators GBDMS. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:269-85.

20. Simpson S, Jr., Wang W, Otahal P, Blizzard L, van der Mei IAF, Taylor BV. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. J Neurol Neurosurg Psychiatry 2019;90:1193-200.

21. Jurynczyk M, Jacob A, Fujihara K, Palace J. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: practical considerations. Pract Neurol 2019;19:187-95.

22. Ghezzi A, Bergamaschi R, Martinelli V, et al. Clinical characteristics, course and prognosis of relapsing Devic′s Neuromyelitis Optica. J Neurol 2004;251:47-52.

23. Jacob A, McKeon A, Nakashima I, et al. Current concept of neuromyelitis optica (NMO) and NMO spectrum disorders. J Neurol Neurosurg Psychiatry 2013;84:922-30.

24. Kim SH, Kim W, Li XF, Jung IJ, Kim HJ. Clinical spectrum of CNS aquaporin-4 autoimmunity. Neurology 2012;78:1179-85.

25. Papais-Alvarenga RM, Carellos SC, Alvarenga MP, Holander C, Bichara RP, Thuler LC. Clinical course of optic neuritis in patients with relapsing neuromyelitis optica. Arch Ophthalmol 2008;126:12-6.

26. Langer-Gould A, Zhang JL, Chung J, Yeung Y, Waubant E, Yao J. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. Neurology 2011;77:1143-8.

27. Dale RC, Tantsis EM, Merheb V, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurol Neuroimmunol Neuroinflamm 2014;1:e12.

28. Hennes EM, Baumann M, Schanda K, et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. Neurology 2017;89:900-8.

29. Ketelslegers IA, Van Pelt DE, Bryde S, et al. Anti-MOG antibodies plead against MS diagnosis in an Acquired Demyelinating Syndromes cohort. Mult Scler 2015;21:1513-20.

30. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain 2017;140:3128-38.

31. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation 2016;13:280.

32. Hino-Fukuyo N, Haginoya K, Nakashima I, et al. Clinical features and long-term outcome of a group of Japanese children with inflammatory central nervous system disorders and seropositivity to myelin-oligodendrocyte glycoprotein antibodies. Brain Dev 2015;37:849-52.

33. Waldman A, Ness J, Pohl D, et al. Pediatric multiple sclerosis: Clinical features and outcome. Neurology 2016;87:S74-81.

34. Jurynczyk M, Geraldes R, Probert F, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 2017;140:617-27.

35. Baumann M, Sahin K, Lechner C, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. J Neurol Neurosurg Psychiatry 2015;86:265-72.

36. Filippi M, Preziosa P, Meani A, et al. Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study. Lancet Neurol 2018;17:133-42.

37. Tintore M, Otero-Romero S, Rio J, et al. Contribution of the symptomatic lesion in establishing MS diagnosis and prognosis. Neurology 2016;87:1368-74.

38. Filippi M, Preziosa P, Banwell BL, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain 2019;142:1858-75.

39. Kitley J, Woodhall M, Waters P, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology 2012;79:1273-7.

40. Salama S, Khan M, Shanechi A, Levy M, Izbudak I. MRI differences between MOG antibody disease and AQP4 NMOSD. Mult Scler 2020:1352458519893093.

국문 요약

후천성 중추신경계 탈수초병은 중추신경계에 면역 관련성 염증 반응 및 탈수초를 일으키는 질환으로 임상적 증상과 영상검사에 따라서 여러 질환으로 분류된다. 최근 말이집 희소돌기아교세포 당단백질 항체를 포함한 생체표지자가 중추 신경계 탈수초 질환의 진단에 각광을 받고 있다. 본 연구에서는 한국 소아 중추 신경계 탈수초 환자에서 뇌척수액내 올리고클론띠, aquaporin 항체, 말이집 희소돌기아교세포 당단백질 항체를 분석함으로써 생체표지자들의 진단적 가치를 알아보고 이와 함께 환자들의 임상 양상과 신경계 영상검사를 분석함으로써 한국 소아 중추 신경계 탈수초 질환의 임상적 특징을 살펴보고자 한다. 혈청 확보가 가능하였던 총 94명의 탈수초 질환 환자들이 포함되었다. 환자들의 인구학적 정보 및 신경계 영상 검사, 뇌척수액내 올리고클론띠, aquaporin 항체, 재발여부, 치료 및 예후를 전자 의무기록지를 통하여 후향적으로 수집하였다. 말이집 희소돌기아교세포 당단백질 항체는 세포기반실험으로 환자들의 혈청에서 확인하였다. 바이오 마커 양성율은 뇌척수액내 올리고클론띠의 경우 45명 중 2명에서, aquaporin 항체는 75명 중 5명에서 말이집 희소돌기아교세포 당단백질은 94명 중 46명에서 양성이 확인되었다. 말이집 희소돌기아교세포 당단백질은 시신경 청수염, 급성 파종성 뇌척수염, 시신경염 뿐 아니라 다발성 경화증 및 진단적 분류가 명확하지 않은 재발성 탈수초 환자에서도 발견되었다. 말이집 희소돌기아교세포 당단백질 항체 양성 환자의 병변은 피질 주위 및 피질하 백질(57%), 시상 및 시상하부(46%), 소뇌(43%), 시신경(46%), 기저핵(39%), 척수(30%) 순으로 광범위하게 분포하였으며 말이집 희소돌기아교세포 당단백질 항체 음성 환자에 비해서 예후가 좋았다($p < 0.001$). 다발성 경화증으로 진단된 환자 중 말이집 희소돌기아교세포 당단백질 양성 환자들은 음성 환자에 비해서 피질의 병변이 자주 확인되었다 ($p = 0.01$). 또한 시신경척

수염으로 진단된 환자의 경우 피질과 피질주위 및 피질하 백질의 병변은 말이집 희소돌기아교세포 당단백질 양성환자에서만 발견되었다. 말이집 희소돌기아교세포 당단백질 항체는 한국 소아 중추신경계 탈수초 질환에서 뇌척수액내 올리고클론띠, aquaporin 항체에 비해서 높은 양성율을 보여 보다 유용하며 다발성 경화증의 진단 전에 시행되어야 하고 정확히 분류되지 않는 재발성 탈수초 질환 환자의 진단에 유용하다. 또한 말이집 희소돌기아교세포 당단백질 양성 환자에서 자주 확인 되는 피질과 피질주위 및 피질하 백질의 병변은 환자를 다발성 경화증으로 오진하게 할 가능성이 있으며 말이집 희소돌기아교세포 당단백질 양성 질환과 aquaporin 항체 양성 시신경척수염의 감별에 유용할 수 있다.

주요어: 탈수초 질환, 생체표지자, 말이집 희소돌기아교세포 당단백질 항체

학번: 2017-34853